

## REFERENCE SHEET:

# Lycopene

## Pronunciation

Lycopene (lie-koh-peen)

## Summary

Lycopene is a non-provitamin A carotenoid that is responsible for the red and pink coloration of certain fruits, such as tomatoes, pink grapefruit, watermelon, papaya, and guava. Lycopene derived from tomato (*Solanum lycopersicum*) sources has been most widely studied and accounts for significant portions of its dietary intake. Additionally, processed tomato products (e.g. ketchup, tomato juice, sauces) containing lycopene are often highly consumed in the U.S.. Of note, processed products, such as ketchup, tomato paste, and spaghetti sauce, contain 16-17 mg/100 g, while fresh tomatoes contain 12 mg/100 g.

Lycopene is most commonly recognized as an antioxidant with roles in preventing oxidative stress in cardiovascular disease, male infertility, osteoporosis, hypertension, neurodegenerative diseases, and inflammatory diseases. Studies have also demonstrated its potential use in prostate conditions, though the limited evidence is not conclusive in its effectiveness.



## Main Medical Uses

Lycopene supplementation can decrease biomarkers of oxidative stress observed in diseases such as CVD or cancer. Evidence supports tomato intake and the use of lycopene supplementation in lowering cardiovascular risk factors in cardiovascular disease, coronary heart disease and metabolic syndrome. Lycopene may be used in treating benign prostatic hyperplasia, asthma, hypertension, hyperlipidemia, leukoplakia, and oral submucous fibrosis, as well as in managing type II diabetes, and infertility. While animal and in vitro studies demonstrate the potential benefits of lycopene for eye health, conflicting epidemiological evidence exists for its use in eye-related conditions, such as age-related macular degeneration and cataracts.

## Proprietary Extracts

Proprietary Extract	Formulation	Safety	Bioavailability
<b>Lyc-o-mato® (Lycored)</b>	Lycopene (6%), $\beta$ -carotene (0.15%), phytoene and phytofluene (1%) and vitamin E (2%), phospholipids (15%) and phytosterol (0.6%) in oleoresin oil.	15 mg per day for 6 weeks, no adverse effects  8 mg per day over 3 months, safe without adverse effects	Equal increase in bioavailability to synthetic lycopene (Lycovit®)  Significant increase in plasma lycopene from oleoresin capsules and tomato juice compared to raw tomato  Equal increase in plasma lycopene from tomato oleoresin, synthetic beadlets and tomato juice
<b>Redivivo®</b>	10% w/w water soluble beadlet. Composed of synthetic crystalline lycopene (all-trans)	Doses up to 30 mg for 8 weeks showed no serious side effects	Doses of 6.5 mg, 15 mg & 30 mg were bioavailable
<b>Lycovit®</b>	10% water-soluble, synthetic beadlets	n/a	Synthetic lycopene (15mg per day, 28 days) had equal bioavailability to tomato-based lycopene (Lyc-o-mato®) in healthy subjects
<b>Lactolycopene (e.g. Ateronon®)</b>	Lycopene (6% - Lyc-o-mato®) within whey protein matrix	n/a	Lactolycopene and tomato paste (supplying 25mg/day of lycopene each), increased lycopene bioavailability equally

## Dosing and Administration

Condition	Dosing & Administration	Outcome	Class of Evidence	Mechanism of Action
<b>Oxidative Stress</b>	30 mg (as Redivivo® synthetic beadlets) per day for 8 weeks	↓ lymphocyte DNA damage & urinary 8-hydroxy deoxyguanosine	B	↓ DNA comet tail length ↓ 8-OHdG ↓ IL-4
	14.64 mg (as Lyc-o-mato® oleoresin tomato extract) per day for 2 weeks	↑ frequency of undamaged DNA, ↓ frequency of damaged DNA in healthy & smoking subjects. ↓ IL-4 in smokers	B	↑ SOD activity, $\beta$ -carotene & LDL-particle size; ↓ hs-CRP, & SBP ↓ lipid & protein peroxidation
	15 mg (unspecified form) per day for 8 weeks	↑ superoxide dismutase activity, endothelial function score, $\beta$ -carotene & LDL-particle size ↓ DNA comet tail length, hs-CRP, & systolic blood pressure	B	
	12 mg (unspecified, synthetic beadlets) per day for 8 weeks	↓ DNA damage	C	
<b>Type II Diabetes</b>	10 mg (unspecified form) per day for 2 months	↑ total antioxidant capacity to malondialdehyde (MDA) ratio.  Significant negative correlation between serum (Ig)G and lycopene, & direct correlation between serum IgM and lycopene	B	↓ MDA, lipid peroxidation  ↑ TAC, macrophage & foam cell formation; ↓ MDA & LDL formation; attenuate T-cell immune response  ↓ LDL oxidation, CRP  ↑ endothelial progenitor cell survival; ↓ apoptosis & oxidative autophagy by advanced glycation end products

Condition	Dosing & Administration	Outcome	Class of Evidence	Mechanism of Action
<b>Cardiovascular Disease</b>	7 mg (as Ateronon® lactolycopene) per day for 2 months	↑ endothelium-dependent vasodilatation by 53% to level of healthy volunteers suggesting improved endothelial function	B	<p>↓ ox-LDL uptake by macrophage &amp; foam cell formation</p> <p>↓ TC, LDL-C, MDA; ↑ HDL-C, glutathione, TG</p> <p>↓ serum NO, ET-1; ↑ VCAM-1, MCP-1, IL-8</p> <p>↓ ICAM-1 expression, TNF <math>\alpha</math> -induced I <math>\kappa</math> B phosphorylation, NF- <math>\kappa</math> B expression, NF- <math>\kappa</math> B p65 translocation, TNF <math>\alpha</math> -induced NF- <math>\kappa</math> B DNA formation, monocyte adhesion to endothelial monolayer</p> <p>↓ PDGF-BB induced PDGFR- <math>\beta</math>, PLC <math>\gamma</math>, and ERK1/2 phosphorylation</p>
<b>Hypertension</b>	15 mg (as Lyc-o-mato® oleoresin tomato extract) per day for 6 weeks	<p>↓ systolic and diastolic BP</p> <p>↑ serum nitrate</p>	B	<p>↓ SBP, DBP; ↑ serum nitrate</p> <p>↓ TBARS</p>
<b>Oral Submucous Fibrosis</b>	4 mg (as Lyc-o-mato® oleoresin tomato extract) twice per day for 2 months	↑ mouth-opening measures	B	<p>↓ juxta-epithelial collagen &amp; inflammation;</p> <p>↑ epithelial thickness</p>
	16 mg (unspecified form) per day for 2 months	↑ mouth-opening measures	B	
<b>Leukoplakia</b>	4-8 mg (unspecified form) per day for 3 months	↑ improvement clinical & histological signs	B	↓ lesion size

Condition	Dosing & Administration	Outcome	Class of Evidence	Mechanism of Action
<b>Osteoporosis</b>	30 mg per (as tomato juice, lycopene-enriched tomato juice, or Lyc-o-mato® oleoresin tomato extract) day for 4 months	↑ total antioxidant capacity ↓ lipid peroxidation, protein oxidation & bone resorption marker NTx	B	↑ total antioxidant capacity ↓ lipid & protein oxidation, & NTx  ↑ bone volume, thickness; ↓ trabecular space  ↓ osteoclast differentiation; ↑ osteoblast proliferation & differentiation  ↑ ALP activity; ↓ bone loss  ↓ osteoclast resorption & ROS production, TRAP & multinucleated osteoclast formation
<b>Benign prostatic hyperplasia</b>	15 mg (as Lycovit® synthetic beadlets) per day for 6 months	↓ PSA & no prostate enlargement	C	↓ PSA & prostate growth  ↑ cell apoptosis  ↓ NAIP, survivin & IL-6 mRNA expression, prostate weight & growth; ↑ caspase-3 expression
<b>Exercise-induced Asthma</b>	30 mg (as Lyc-o-mato® oleoresin tomato extract) per day	↑ protection against asthma	C	↓ airway neutrophil influx, neutrophil elastase activity  ↓ inflammatory immunocytes, gelatinolytic activity, eosinophil peroxidase & IL-4 expression, & GATA-3 mRNA  ↓ eosinophilic infiltrates, IL-4 & IL-5
<b>Male Infertility</b>	20 mg (unknown form) per day for 12 weeks	↓ soluble receptor for advanced glycation end products (sRAGE) in seminal plasma in fertile and infertile subjects	C	↓ sRAGE in seminal plasma  ↑ bactericidal activity  ↑ antioxidants, sperm concentration, count, motility, morphology, viability; ↓ lipid peroxidation, DNA damage

## Associated Depletions and Interactions

Class of Drug	Pharmaceutical	Effect	Class of Evidence
<b>Statins</b>	Unspecified; mean equivalent dose of 40 mg of simvastatin)	↑ endothelium-dependent vasodilatation with lycopene (7 mg per day for 2 months) compared to placebo	B
<b>ACE inhibitors</b>	Enalapril (10 mg)	↓ systolic and diastolic BP ↑ serum nitrate (means grouped with other drug groups) with lycopene (15 mg per day for 6 weeks) compared with placebo	B
<b>Calcium Channel Blockers</b>	Amlodipine (5mg)	↓ systolic and diastolic BP ↑ serum nitrate (means grouped with other drug groups) with lycopene (15 mg per day for 6 weeks) compared with placebo	B
<b>B-blockers</b>	Atenolol (25 mg)	↓ systolic and diastolic BP ↑ serum nitrate (means grouped with other drug groups) with lycopene (15 mg per day for 6 weeks) compared with placebo	B
<b>Diuretics</b>	Hydrochlorothiazide (12.5 mg) in combination with Enalapril (10 mg), Amlodipine (5mg), or Atenolol (25 mg)	↓ systolic and diastolic BP ↑ serum nitrate (means grouped with other drug groups) with lycopene (15 mg per day for 6 weeks) compared with placebo	B
<b>Alcohol</b>	Ethanol (27% and 36% of total calories)	↓ alcohol-induced steatosis, hepatic inflammatory foci, and CYP2E1 protein level by tomato powder. ↑ 3.7-fold in hepatic inflammatory foci in lycopene (1.1 mg/kg) group in rats & no change in CYP2E1 mRNA	D
	Ethanol (36% of total calories)	↑ CYP2E1 expression, TNF $\alpha$ mRNA & inflammatory foci with lycopene (3.3 mg/kg) combination compared to alcohol alone. ↓ cis isomer lycopene in plasma & liver	D
<b>Minerals</b>	Calcium (500mg)	↓ plasma lycopene (19mg from tomato paste) compared with non-calcium group	D

Class of Drug	Pharmaceutical	Effect	Class of Evidence
<b>Herbicides</b>	Atrazine (50 or 200mg/kg)	Lycopene (5mg/kg) modulates CYP450 levels & activity, and normalized mRNA expression of hepatic, CYP2A4 previously increased by atrazine. Normalizes CYP1B1, CYP2E1 & CYP4A14 previously increased by atrazine (protecting against toxicity)	D
<b>Carotenoids</b>	$\beta$ -Carotene (single dose of 60mg)	↑ AUC of lycopene (60mg) when co-administered compared with alone. No effect on $\beta$ -Carotene with co-administration compared to $\beta$ -Carotene alone.	D
	Lutein (11.93g from spinach or 12 mg from tablet per day, 3 weeks)	↑ plasma lycopene (14.98g from tomato paste) by 85% and 92% with spinach or lutein pills compared with 16% increase from tomato paste alone from baseline. No effect of adding tomato paste (14.98g lycopene) or tablet (15mg lycopene) on change in lutein status	D
<b>Antiplatelet</b>	Aspirin (140 $\mu$ mol/L and 70 $\mu$ mol/L)	↓ platelet aggregation induced by ADP and collagen with combination lycopene (4 $\mu$ mol/L) compared with Aspirin (140 $\mu$ mol/L) alone	E

For an explanation of the classes of evidence, please see the [Rating Scales](#) for Evidence-Based Decision Support.

## Adverse Effects

The observed level of safety for lycopene has been described at 75mg per day, though higher concentrations have been ingested without adverse effects. Doses of lycopene as high as 120 mg per day have been ingested without adverse effects in healthy subjects and has been shown to be safe at this dose after a year of consumption. Rare instances of allergic skin reactions have been reported.

### Mechanism of Action and Metabolism

Approximately 10-30% of lycopene is absorbed after oral intake via passive diffusion in the intestine and by the scavenger receptor class B type I (SR-BI) cholesterol membrane transporter. Lycopene is distributed in highest concentrations to the testes, and then sequentially to the adrenals, liver, prostate, breast, pancreas, skin, colon, ovaries, lungs, stomach, kidney, adipose tissues, and cervix, thereafter. Lycopene may moderately inhibit CYP2E1, CYP1A1 and CYP1B1 and increase microsomal uridine diphosphate (UDP)-glucuronosyltransferases (UGT) activity. It appears to be metabolised by  $\beta$ -carotene 9',10'-oxygenase (BCO2) to apo-10'-lycopenal, oxidized to apo-10'-lycopenoic acid, reduced to apo-10'-lycopenol thereafter, or metabolized to CO<sub>2</sub> via  $\beta$ -oxidation before urinary excretion.

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